DOI:
10.1016/j.cct.2016.12.003

Document Version
Peer reviewed version

Effectiveness of adjunctive, personalised psychosocial intervention for non-response to opioid agonist treatment: study protocol for a pragmatic randomised controlled trial

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Abstract: 250 words
Main text: 6,969 words
Tables: 2
Total pages in manuscript: 24

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KEYWORDS: heroin; cocaine; opioid substitution; psychosocial; trial

ABSTRACT

INTRODUCTION: Opioid use disorder (OUD) is a debilitating and relapsing psychiatric disorder; opioid agonist therapy (OAT) is the front-line, evidence-supported treatment. A substantial number of patients relapse or continue to use heroin or other illicit drugs during OAT. There is considerable heterogeneity in the OAT-resistant sub-population, with many behavioural moderators of treatment response. We have developed a personalised psychosocial intervention (PSI) targeting these individuals. A formulation-guided assessment is linked to a toolkit of motivational, cognitive/behavioural and social support techniques. Change methods have been adapted from evidence-supported psychological therapies and are idiosyncratically tailored to the need and response.

METHODS: In this single-centre, 18-week, parallel group, pragmatic randomised clinical trial, we will determine the clinical and cost-effectiveness of the PSI as an adjunctive intervention during OAT, in comparison to opioid agonist treatment-as-usual. We plan to recruit 368 adults. The primary outcome measure is the proportion of participants categorised as 'responders' at the end of the intervention (defined as self-reported abstinence from heroin and cocaine with no positive biological drug tests during the 28 days prior to the endpoint). Secondary outcomes include: percentage of days abstinent from heroin and cocaine in the 28 days before follow-up; treatment retention; therapy compliance; health and social functioning; exploratory genetic biomarkers; and analyses of treatment moderation and mediation.

CONCLUSIONS: This pragmatic controlled trial determines the effectiveness and cost-effectiveness of a personalised PSI for non-responding patients during OAT. Our intervention applies motivational, cognitive/behavioural and social support techniques adapted from evidence-based therapies. Findings will inform stratified delivery of OAT.

1. INTRODUCTION

Non-medical opioid use is an important contributor to the global burden of disease [1]. Opioid use disorder (OUD) is a debilitating and relapsing psychiatric condition characterised by compulsive drug taking, despite significant adverse physical and psychosocial consequences [2]. Oral opioid agonist therapy (OAT) is the front-line medication assisted treatment, offering medical management of physiological dependence and access to medical and social care. Systematic reviews of randomised controlled trials show that OAT is effective - with marked reductions in illicit drug use and drug injecting, and a high level of retention in treatment [3,4,5]. However, a significant minority of individuals do not stop using illicit drugs during OAT [6,7]. For example, using national data in England, we observed that between 26-33% of patients did not reduce heroin use after 6 months of treatment, and 3% deteriorated to more frequent levels than at admission [8].

Our work in community addiction clinics points to three OAT-resistant groups: *intermittent responders* - patients who stop or substantially reduce drug use in the first few weeks, but then relapse and cycle through periods of unsanctioned exit and re-admission; *brief responders* - patients who achieve only short periods of reduced drug use; and *poor responders* - patients who do not achieve any significant reductions in their illicit drug use, although they may stay in treatment for longer than average. Patients from these sub-populations might benefit from psychosocial interventions. However, systematic review evidence shows that specific adjunctive psychosocial interventions to date have not been able to increase treatment retention or help patients reduce drug use [9].

Against this background, we contend that an idiosyncratic approach has the best chance of success. Our conceptualisation of addiction treatment unites three constructs: the severity of addiction symptoms, health and social problem complexity, and the patient's personal recovery strengths. We have shown than in the day-to-day operation of addition clinics these constructs predict treatment response: patients with higher ratings of addiction and concurrent problem complexity are more likely to be using heroin or cocaine at follow-up, and those with more personal strengths are more likely to have achieved stable abstinence [10]. We have designed the current study to produce results that can be generalised and applied to routine practice settings. In this protocol paper, we describe the rationale, methods, analyses, strengths and limitations for a pragmatic randomised controlled trial (RCT) of personalised psychosocial intervention (PSI) during OAT to help patients abstain from heroin and cocaine (Addiction Recovery Clinic Trial [the ARC Trial]).

2. METHODS

2.1 Study design

The ARC Trial is a single-centre, 18-week, parallel-group, pragmatic RCT of standard care OAT plus PSI, compared to standard care OAT. It has been designed to conform to the CONSORT guideline extension for such trials [11], and the Template for Intervention Description and Replication (TIDierR) checklist for reporting interventions [12].

The study is registered (ISRCTN number: 69313751) and will be conducted according to the ethical principles of the Declaration of Helsinki (1996), with all members of the study team trained in accordance with Good Clinical Practice. Participant materials, study protocol and clinical research forms have been reviewed and approved by the London-Bromley Research Ethics Committee (reference: REC 13/LO/0640; granted 05.06.2013; first participant enrolled on 07.06.2013).

2.2 Study aims

Among patients who have received six or more weeks of OAT and are currently using illicit heroin or cocaine[1], the primary aim of the study is to determine the effectiveness and cost-effectiveness (see section 2.13.5) of OAT with a 12-week, adjunctive PSI to help patients abstain from heroin and cocaine. The comparison condition is OAT with standard case management (the treatment-as-usual condition; TAU).

The secondary aims of the trial are to estimate the effectiveness of the PSI as evidenced by self-reported heroin and cocaine use, treatment retention, intervention adherence, craving response for heroin and cocaine, quality adjusted life years, and may include description of longer-term criminal offending and mortality. There will be exploratory analyses of treatment moderation and mediation using clinical measures, and targeted analyses of genetic biomarkers of treatment response.

2.3 OAT treatment, setting and study population

Current United Kingdom (UK) clinical guidelines recommend the following front-line oral opioid agonist medications: methadone (mu opioid receptor (μOR) agonist: 60-120mg/day during the post-induction maintenance phase); and buprenorphine (partial μOR: 12-32mg/day during maintenance; also available as a 4:1 buprenorphine-naloxone formulation).

[1] In the UK illicit opioid using population, the smokeable base form of cocaine [colloquially known as *crack*] rather than the powder version is most commonly available.

The trial will be conducted at a specialist National Health Service (NHS) community addiction treatment centre in London operated by South London and Maudsley NHS Mental Health Foundation Trust. The centre admits ~15 patients per month into OAT. This is delivered by a multi-disciplinary team including psychiatry, psychiatric nursing, psychology and social work specialties. OAT patients are assigned to a member of the clinical team (known as a *keyworker* in the UK treatment system) for case co-ordination, general counselling and support.
The study population are adults with clinically confirmed opioid use disorder (OUD; DSM-IV [2]) who have been enrolled in oral methadone, or oral buprenorphine, or oral buprenorphine-naloxone OAT at the centre for at least six weeks and are classified as non-responders (operationally defined for the trial as continuing [or relapsing] to use heroin or cocaine use, with biological verification of recent drug use).

We plan to recruit 368 adults. The study is estimated to take 3.5 years to complete, as follows: participant recruitment to month 30; clinical data collection completed by month 36; and data management and analysis completed by month 42.

2.4 Patient eligibility and enrolment

Participant inclusion and exclusion criteria for the study are summarised in **Table 1**.

[Table 1, about here]

Keyworkers will refer patients to the ARC Trial research team based at the centre. Electronic patient records will also be used to identify potential participants. At a screening visit (~30 minutes to complete), a brief medical and social history will be recorded, including OAT medication check, current use of heroin and cocaine, collection of stratification factors (see section 2.6), and obtaining informed consent to access OAT medication, concomitant psychiatric medication, treatment retention and adherence information (from the electronic patient record)[2].

During screening, the visit to record baseline measures, and the outcome endpoint assessments (all conducted at the centre), participants will be asked to provide a urine sample. This will be tested for the major metabolites of heroin (morphine), cocaine (benzolyecgonine), and benzodiazepines (the latter for sample descriptive purposes). A tamper-proof, 48-hour

[2] Criminal convictions and mortality data (from the police national computer and UK deaths register, respectively) will be collected in the longer-term and are not addressed further in this paper.

detection window, instant result urine drug screen (UDS) device will be used (Integrated E-Z Split Key Cup; www.concateno.com). For a valid test, the device's temperature sensor will be required to register 92°-96°F.

As part of the UDS administration process, a clinical interview will record self-reported days heroin, other illicit/non-medical opioids, cocaine, alcohol and non-prescribed sedative/anxiolytic [benzodiazepine] medication use in the previous 28 days (drug use section of the Treatment Outcomes Profile; [TOP; 13]). The TOP is the standard national instrument for monitoring the outcomes of substance use disorder treatment in England. It uses a structured, calendar-prompt, timeline follow-back [TFLB] procedure for recall of drug consumption [14].

2.5 Assessments

The following psychometrically robust measures will be administered prior to randomisation (baseline) and also during the intervention and at outcome (as shown in parentheses) and summarised in **Table 2**:

[Table 2, about here]

2.5.1 MINI international neuropsychiatric interview (DSM-IV and ICD-10 disorders; MINI; [15]; baseline). The MINI is a structured diagnostic assessment for diagnosis of the following current disorders (past year, unless otherwise stated): alcohol, opioid, cocaine use disorder; major depression; panic; post-traumatic stress; generalized anxiety; and anti-social personality (lifetime).

2.5.2 Personality Disorder Screen (PDS; [16]; baseline). The PDS is a 38-item checklist (response: true/false) from the World Health Organization's Composite International Diagnostic Interview to characterise maladaptive personality traits.

2.5.3 Buss-Perry Aggression Questionnaire (BPAQ-Short-Form; [17]; baseline). The BPAQ-SF is a 12-item scale which records expression of aggressive traits. It is the short-form of the 29-item Aggression Questionnaire [18].

2.5.4 Barratt Impulsiveness Scale (BIS-11; [19]; baseline). The BIS-11 is a 30-item scale which assesses personality and behavioural aspects of impulsiveness. The BIS-11 has sub-scales for the following latent constructs: attention, cognitive instability, motor, perseverance, self-control, and cognitive complexity.

2.5.5 Montreal Cognitive Assessment (MoCA; [20]; baseline [version 7.1]; final follow-up [version 7.2]): The MoCA is a brief screening instrument for mild cognitive impairment and assesses attention, concentration, working memory, visuo-constructional skills, and conceptual thinking. A score of ≥26 is considered to reflect normal range functioning. An alternate version of the MoCA will be used at the study endpoint to decrease the risk of learning effects from baseline administration.

2.5.6 Minnesota Craving Scale [21]; baseline, and follow-ups). The Minnesota Craving Scale will be adapted to assess craving response for heroin (labelled MCS-H) and cocaine (MCS-C). This 5-item scale records the intensity, frequency and duration of craving episodes in the past week.

2.5.7 Patient Health Questionnaire (PHQ-9; [22]; baseline and final follow-up). The PHQ-9 is a brief scale which assesses the frequency of depressive symptoms during in past two weeks.

2.5.8 Generalized Anxiety Disorder Scale (GAD-7; [23]; baseline and final follow-up). The GAD-7 is a brief scale which assesses the frequency of anxious thinking in the past two weeks.

2.5.9 Work and Social Adjustment Scale (WSAS; [24]; baseline and final follow-up). The WSAS is a 5-item scale which records the extent of social functioning impairment caused by clinical problems in the past two weeks.

2.5.10 Adult Service Use Schedule (AD-SUS; [25]; baseline and final follow-up). The AD-SUS is a structured interview to record patient-level health and social care resource use. It has been used in treatment trials with the target population. Information on services received at the centre and other services will also be recorded from the electronic patient record.

2.5.11 EQ-5D-3L ([26]; baseline and final follow-up). The EQ-5D-3L is a brief generic scale which captures health-related quality of life (HRQoL) on five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and with a 20cm vertical visual analogue scale. These responses are combined to yield a five-digit rating of HRQoL.

2.5.12 Session Rating Scale (SRS; [27]; baseline and all follow-ups [PSI participants only]). The SRS is a 4-item visual analogue rating scale which records the participant's rating of therapeutic alliance with the therapist. The SRS will be used as a measure of PSI session quality.

2.5.13 Outcome Rating Scale (ORS; [28]; baseline and all follow-ups [PSI participants only]). The ORS is a 4-item scale which records the patient's evaluation of their intra/interpersonal and social functioning. The ORS will be used as an evaluation of the perceived PSI effectiveness.

2.5.14 Molecular biomarker screening; baseline and final follow-up. Using a separate consent process, study participants in the study will be invited to provide a sample of oral fluid for genotyping of biomarkers of treatment response. A pre-packed set of 10 cotton 'Q-Tip' buds will be used for sample collection. Biological samples will be sealed in a barcoded, 15cm plastic collection tube containing 10ml neutral buffer solution. DNA extraction and storage will be done at the Social, Genetic and Developmental Psychiatric Centre at the Institute of Psychiatry, Psychology and Neuroscience, King's College London.

2.6 Participant randomisation

Following completion of baseline measures, participant randomisation will be initiated. This procedure will be independently managed by the King's College London Clinical Trials Unit (King's CTU; www.ctu.co.uk) using a web-accessed computer programme on the King's CTU server. Study participants will be randomised on a 1:1 basis to one of the two study conditions using block randomisation (randomly varying block sizes) with the following binary stratification factors (coded for the 28 days prior to baseline): cocaine use, non-medical drug injecting, and OAT medication (methadone or buprenorphine).

The randomisation procedure will be initiated by the ARC team at the centre using a unique participant identification number (PIN) and password. The participant's initials, date of birth, study PIN and stratification information will then be entered on the randomisation database. The system will then automatically allocate the participant to the PSI or TAU intervention and generate a confirmation email.

2.7 Treatment-as-usual

Study participants who are allocated to TAU control condition will continue to receive OAT with standard fortnightly case management appointments with their keyworker at the centre, for up to 15 weeks during the study. Each of these appointments will last ~30 minutes and will include a medication adherence review, provision of harm reduction advice, counselling, and support to receive local health and social care services.

For participants allocated to the TAU condition, the active period of assessment will commence six week's post-randomisation to align with the timing of the PSI intervention. During TAU, there

may be alterations to the participant's OAT dose or medication, which reflects routine practice. ARC Trial research assistants will meet with TAU participants in a clinical interview room at the centre to complete all outcome assessments during the intervention and at the endpoint.

2.8 Theoretical framework for the experimental intervention

Convergent lines of epidemiologic and clinical research point to several behavioural factors which moderate OAT effectiveness [29]. Addiction severity is moderator [30,31,32], and taking illicit drugs by injection correlates with higher levels of dependence and a likelihood of non-response [33]. Concurrent cocaine use and dependence is also common among the OUD population in the UK, and these patients tend to have poorer engagement with the clinic and outcome [34,35,36]. A significant minority of patients have co-existing chronic health and social problems which follow, precede, or are independent of the addictive disorder, and add complexity to clinical management [37,38,39]. The patient's family relationships and social networks may also support or hinder response [40]. We screen for these factors early in treatment.

The PSI is founded on the evidence that there are different reasons for OAT non-response and that there will be no single best clinical response. Our goal is to help the patient reduce the symptoms of heroin and cocaine addiction, to manage or attenuate concurrent health and social problems, to enhance engagement with OAT, and to develop personal strengths and resources for recovery.

2.9 Personalised psychosocial intervention

Participants who are allocated to the PSI will continue to receive OAT and standard case management (fortnightly keyworker sessions ~30 minutes' duration and regular medical reviews) during the study. The PSI will be delivered by the clinical psychology team at the centre under the supervision of the Lead Investigator (L.M) and Chief Investigator (J.M.) and working with the medical director (author M.K.), centre physicians, and keyworkers to optimise OAT medication. The evaluated PSI will be collaborative and flexible: trial psychologists will use a non-judgemental, collaborative counselling style (adapted from Motivational Interviewing [41]) and graphical representations and maps (adapted from node-link mapping to facilitate assessment, care planning, and progress review [42]. Our PSI represents a point of departure from a traditional manual-guided psychological therapy in which there may be proscription of a sequence of specific techniques, or multi-modal therapies which combine two or more therapies. We will use a 'toolkit' approach with specific change methods from evidence-supported therapies are chosen collaboratively with the patient and tested for effectiveness in

the form of a rolling set of behavioural experiments. During development, we reviewed national clinical guidelines [43] and the therapist manuals for the following psychological therapies:

- cognitive behavioural coping and skills training (CBT [44]);
- behavioural reinforcement ('contingency management' using shop vouchers with clinic attendance and recovery activities in addition to the traditional drug abstinence operant reinforcer [45];
- behavioural psychotherapy for couples to promote relationship stability and abstinence reinforcement [46],
- Social Behaviour and Network Therapy to recruit family members and others to accompany the patient to PSI sessions and support their recovery [47,48];
- 12-Step Facilitation Therapy for self-help group attendance [49,50]; and
- CBT methods for depression to help raise awareness of automatic thoughts, depressive evaluations and increase activity [51].

We selected a set of cognitive and behavioural change techniques described in these manuals and adapted them to our target population. Each PSI intervention will include two or more of these specific change techniques, with supporting participant informational and self-monitoring materials.

Participants will be invited to attend an initial formulation session (~60 minutes) with a graduate or masters trained Assistant Psychologist (AP) or Senior Psychologist (SP). This session will be completed no later than six weeks after the participant has been randomised. The aim will be to developed an idiosyncratic conceptualisation of how heroin and/or cocaine use is being maintained during OAT, with review of the participant's drug-related cognitions, motivations, drug use behaviours, and evaluations. This conceptualisation will be informed by the study baseline assessment battery, and the care plan will be adjusted according to response (i.e. to build on improvements in drug use behaviours, prevent relapse, or select different methods in the event of continued illicit drug use).

A care plan for each participant will be brought to a weekly clinical case conference attended by all trial therapists with trial leads L.M. and J.M. in attendance. The participant will be invited to attend a programme of weekly, 60-minute, face-to-face sessions over the following 12 weeks at the centre with the AP. We will use brief telephone support and phone text messages to confirm appointments. Two additional weeks may be added to the PSI to replace missed sessions with advance notification (e.g. due to illness, outpatient appointments, inpatient stays, therapist absence and so on).

For those with no clinically significant cognitive impairment, the PSI typically starts with a focus on links between drug-related cognitions, behaviours and consequences [52,53]. For those patients with significant cognitive difficulties, contingency management may precede work on these addiction sequelae. If the participant is depressed, the PSI may be implemented as twice-weekly sessions with a shorter duration (~30 minutes) to facilitate attention, engagement and clinical effectiveness. ARC Trial research assistants will meet with PSI participants in a clinical interview room at the centre to complete outcome assessments during the intervention and at the endpoint.

2.10 Treatment monitoring and fidelity

As part of our efforts to ensure that the PSI is delivered with integrity, each session will be audio recorded (subject to permission) and the therapist will complete a content checklist of the specific techniques used in the session from the toolkit. In addition to personal supervision, study therapists will attend a weekly case conference with trial leads L.M. and J.M. and other SPs. ARC therapists will discuss practice questions using selected audio excerpts from PSI sessions. A random 5% sample of session recordings will be independently rated using the Cognitive Therapy Scale-Revised [54].

2.11 Outcome measures

2.11.1 Primary outcome

The primary outcome measure will be recorded during a structured follow-up interview by a research assistant working independently from the clinical team as the proportion of participants who: (a) report no use of heroin or cocaine during the 28 days prior to the final follow-up interview after the 12-week intervention period and: (b) provide one or more negative UDS tests for heroin and cocaine in the 28 days prior to final follow-up and no positive tests. Patients who meet these criteria will be categorised as 'responders' on the primary outcome measure.

2.11.2 Secondary outcomes

The secondary outcomes are: (1) percentage of self-reported heroin and cocaine abstinent days during the 28 days prior to final follow-up interview; (2) treatment retention (defined as the number of days from randomisation to treatment exit); (3) treatment compliance (operationalised as attendance at one-third or more scheduled sessions); (4) follow-up score on MoCA[3], PHQ-9, GAD-7, WSAS, AD-SUS and EQ-5D-3L (see section: 2.13.5 for economic analysis).

[3] Proportion of participants falling within the normal range on the MoCA.

2.12 Sample size calculation

From a meta-analysis of psychological interventions for substance use disorders, we estimate that the proportion of participants classified as 'responders' after the intervention period will be approximately 0.24 in the TAU and 0.42 in the PSI treatment arm [42]. We judge this to be a clinically significant difference.

Allowing for 16% attrition (the typical rate from OAT reported by the English National Drug Treatment Monitoring System), an overall sample size of 368 participants will be sought. We estimate that a sample of 184 participants allocated to the PSI and 184 allocated to TAU will give 90% power to detect the anticipated 18% difference in responder status using a two-sided 5% significance test.

[**Table 2 about here**]

2.13 Statistical analyses

All analyses will be pragmatic and follow the intention to treat principle, with participants analysed in the group they were randomised irrespective of the duration, intensity, or quality of treatment received, utilising all available post-randomisation follow-up data.

There are no planned interim analyses. All analyses will be completed in Stata 14 using two-sided 5% significance tests. Main intervention effects will be summarised by study arm and assessment time point, with associated 95% confidence intervals.

Reflecting the pragmatic nature of the study, we expect some participants to drop out of treatment and then be readmitted. If a participant decides to withdraw from the study, we will use the data collected to that point unless otherwise requested by the participant.

2.13.1 Primary analysis

The main objective of the analysis is to assess the effect of the personalised PSI on the primary outcome measure. Using TOP and UDS data collected at the 4, 8 and 12-week post-randomisation follow-up, we will create a binary response outcome for each participant: self-reported abstinence from heroin, illicit/non-medical opioids and cocaine for the preceding 28 days, with no positive UDS tests, assessed up to 18-weeks post-randomisation (i.e. 6 weeks for pre-intervention case conceptualisation and treatment formulation and 12 weeks of treatment).

A mixed-effects logistic regression model (Stata command *meqrlogit*) will be fitted for the primary analysis, with the following covariates: stratification factors (baseline cocaine use, non-

medical injecting, OAT medication), treatment arm (PSI or TAU). We will fit a treatment x time interaction term, the time of outcome assessment (days post-randomisation and using a quadratic function if statistically significant), and a participant-varying random intercept and slope (if this significantly improves model fit). A linear combination of model coefficients will be used to estimate PSI effectiveness (Stata command *lincom*).

2.13.2 Secondary analyses

The secondary analyses (percentage of self-reported days abstinent from heroin and cocaine in the 28 days before final endpoint; treatment retention [days enrolled in treatment], drug use craving response [monthly], and the SRS and ORS session ratings) will be undertaken within a generalised linear model framework. These models will include the baseline measure (if applicable), the stratification factors and treatment arm as covariates.

Where assumptions of normality do not prove to be applicable for the outcome measure, we will use Poisson and other extensions to ordinary linear regression models. Between treatment retention and adherence will be evaluated with Kaplan-Meier curves and log-rank analyses. A chi-squared (Fisher's exact) test will be used to assess adverse events (see section 2.14).

2.13.3 Exploratory moderation and mediation analyses

We will estimate the moderating (interaction by trial arm) effect on the primary outcome measure and the drug use, treatment retention and treatment adherence secondary outcomes for sub-populations identified using the following baseline measures: MINI psychological and substance use disorders (major depressive; suicidality; panic; post-traumatic stress; anti-social personality; opioid; cocaine; alcohol); PBS, BPAQ-SF and the BIS-11 [55]. Following established methods, interaction terms will be centred and orthogonalised [56].

Change in monthly scores on the MCS-H and MCS-C and alterations in OAT medication will be investigated as mediators of treatment effect.

2.13.4 Sensitivity analysis and management of missing data

Missing observations are expected in the dataset. The analyses will be based on maximum likelihood and provide valid inferences under a missing at random (MAR) assumption. In this context, we will empirically assess whether baseline assessments predict missingness and include predictors as covariates in the analysis models. A commonly used strategy in the field is to record missing UDS information as positive (penalized imputation). Sensitivity analyses will

use this approach and also assess the robustness of conclusions to missing outcome data and to departures from randomised treatment.

2.13.5 Cost-effectiveness analysis

The cost-effectiveness evaluation will take a broad, societal perspective including the impact of treatment on the use of all health and social services, criminal justice sector resources and productivity losses (time off work due to illness). The cost of the PSI therapy will be directly calculated taking a micro-costing approach. A cost per-hour of each therapist, including employer costs (National Insurance and superannuation contributions), overhead costs (capital, administrative and managerial etc.) and supervisor costs, will be applied to data on direct face-to-face contact and indirect time (supervision, training, preparation). Indirect time will be estimated using information provided by trial therapists on the ratio of time spent in face-to-face contact to time spent on other activities. Resource use will be valued using national tariffs/units and National Health Service reference costs and applied to all services external to the centre. The cost of OAT and concomitant medication will be taken from the British National Formulary.

The human capital approach will be applied to value productivity losses [57]. The cost of criminal activity will be obtained from Home Office estimates [58]. Unit costs will be multiplied by the corresponding service use data to generate total costs per participant. Cost differences will be analysed using *t*-tests with the validity confirmed by bias-corrected, non-parametric bootstrapping (i.e. repeat re-sampling [59]). All economic analyses will be adjusted for the study stratification factors plus baseline values of the variable of interest. Cost-effectiveness will be estimated using the primary outcome measure.

Secondary analysis will use quality adjusted life years calculated using the EQ-5D-3L [60]. Cost-effectiveness will also be assessed by estimating incremental cost-effectiveness ratios. A joint distribution of incremental mean costs and effects for the two groups will be generated using non-parametric bootstrapping to explore the probability that the PSI or TAU is the better choice. Uncertainty around the cost and effectiveness estimates will be represented by cost-effectiveness acceptability curves [61].

2.13.6 Exploratory genetic association analysis

In this study of OAT treatment response, we will use a stress-response and relapse risk approach within an epigenetic framework to guide targeted, exploratory SNP association analyses from biological samples collected at baseline and at final follow-up. Reflecting the relatively small-scale nature of the trial, hypothesis testing will be targeted and the analysis

limited to dopaminergic, serotonergic, adrenergic and GABAergic biomarkers of outcome response. For example, we will assess for SNP variants of the FKBP5-binding protein 51 (a modulator of glucocorticoid receptor activity [62]) and the alpha-1 adrenoreceptor (ADRA1A; [63]). We will include these biomarkers in exploratory analyses of treatment moderation and mediation alongside targeted clinical measures and the classification of treatment response.

All genetic association analysis will be conducted by laboratory collaborators who will be blind to trial arm. Our analysis plan may be updated for ancillary studies within this general framework in accordance with emergent genetic and epigenetic biological evidence.

2.14 Data management, monitoring and study governance

Participants' personal data will be stored securely within the centre in individualised source data worksheets. Electronic case reports will be created in which participants will be identified by a unique code and initials (using the commercial data entry system: InferMed MACRO; https://www.elsevier.com/solutions/infermed). After completion of all follow-ups and prompt entry of data, the dataset will be reviewed for accuracy and then locked for analysis. The statistical analysis plan will be finalised and approved prior to treatment arm allocation unmasking. In addition to recording adverse events, each participant will be asked during the final follow-up research interview whether they have experienced anything particularly harmful or distressing during the study and if so, whether they believe it was related or caused by the interventions and procedures. This assessment will be supplemented by a review of the clinical record. All adverse events, adverse reactions, and serious and unexpected adverse events and reactions, will be recorded and reported immediately.

A Data Monitoring Committee will review recruitment and safety data during the trial and report to a Trial Steering Committee (TSC). The TSC and DMEC will be independent from the sponsor and funders, and will include a statistician, clinician and clinician scientist. These committees will convene every 6-12 months.

3. DISCUSSION

As we progress into a fifth decade since buprenorphine was discovered and methadone introduced, we judge that there is a strong imperative to develop and evaluate adjunctive, personalised psychosocial interventions for people who do not respond to OAT. The ARC Trial is a pragmatic study of OAT in a routine clinic setting which targets patients who continue to use heroin or cocaine after a minimum of 6 weeks. Finding effective means of helping these hard-to-

reach patients is important. A recent study observed that non-medical opioid use during the first two weeks of OAT was strongly predictive of an unsuccessful outcome at 12 weeks [64].

We think our study has several strengths. First, the ARC Trial is open to as many members of the target population as possible, while protecting safety and likelihood of follow-up. Secondly, our primary outcome is a well-defined, clinically meaningful and stringent, and all secondary outcomes are recorded using validated scales. The collection of outcome measures is timed to coincide with routine clinical follow-up as part of our efforts to minimise loss to follow-up.

Thirdly, we will make pragmatic use of various psychological change techniques rather than a fixed therapeutic manual. This allows the therapist considerable flexibility, and reflects a problem-service matching approach which has been promoted to direct participants to specific medical care and psychological interventions and supports.

We also acknowledge several limitations. First, our findings will be limited to application in substance use disorder treatment centres with access to appropriately trained and supported psychologists and psychotherapists. Secondly, the primary outcome measure was selected to reflect the aim of the PSI and not rely on self-report; but it may be may be too stringent. There is no consensus in the illicit drug treatment field for outcome measurement, although the percentage of abstinent days during a follow-up period is often used (and is used in this study as a secondary outcome measure). It is likely that some participants who are classified as non-responders on the primary outcome will report a reduction in drug use and our secondary analyses will address this response gradient.

An integrated approach to assessment, stratified treatment and continuing care is now gaining momentum in behavioural medicine, where tailoring variables and decision rules are improving outcomes [65]. We expect the ARC Trial to contribute to this applied orientation in the addictions.

AUTHORS' CONTRIBUTIONS

J.M. (chief investigator) developed the concept and study design with L.M. (lead investigator) and M.K, with input from G.S., C.M. and J.H. The statistical analysis plan was developed by J.H. J.M., G.S. and J.H. drafted the manuscript with input from all authors. All authors read and approved the final version before submission for publication.

FUNDING AND SPONSOR

The ARC Trial is funded by an investigator-led, educational grant from Indivior PLC, administered by Action-on-Addiction (J.M. Chief Investigator and L.M Lead Investigator). The funder had no role in the study design or the writing of this protocol paper. The contents of this report do not necessarily reflect the views or stated position of Indivior or Action-on-Addiction. King's College London (KCL) and South London and Maudsley NHS Mental Health Foundation Trust will act as the joint study sponsors. KCL is the holder of the study's indemnity insurance policy.

COMPETING INTERESTS

J.M. is supported by research grants from the Department of Health, Institute for Health Research (NIHR), and the NIHR Biomedical Research Centre for Mental Health. He has part-time employment as Senior Academic Advisor for the Alcohol, Drugs and Tobacco Division, Health and Wellbeing Directorate, Public Health England. He declares grant funding at IoPPN and SLaM MHFT from NIHR (HTA) for a trial of extended-release naltrexone; honoraria from Merck Serono (2013, 2015; clinical oncology medicine), and Indivior (via PCM Scientific) as faculty member (2012-2013), co-chair (2015-2016) and chair (2017) for the Improving Outcomes in Treatment of Opioid Dependence conference.

J.H. is part supported by the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London.

All other authors declare no competing interests.

ACKNOWLEDGEMENTS

We kindly acknowledge the following people for their support. *TSC members*: Edward Day (Chair); Peter Burkinshaw; Christopher Whiteley; Paul Lennon; *Data Monitoring Committee members*: Richard Holland (Chair); Edward Juszczak; Rick Rutkowski; *Study funder*: Danilo Lembo (Indivior PLC); Amanda Thomson, Nick Barton (Action-on-Addiction); *Kings Clinical Trials Unit at King's Health Partners*: Beverley White-Alao, Gill Lambert; SLaMHFT/Institute of Psychiatry, Psychology and Neuroscience (IoPPN) R&D office: Jenny Leibscher; *Department of Biostatistics, IoPPN*: Andrew Pickles.

Table 1

Participant inclusion and exclusion criteria

Inclusion criteria:

In order for a participant to be enrolled into the study they must fulfil all of the following inclusion criteria:

(a) Aged 18≥ years (no upper limit, but usually less than 60 years);

(b) Current diagnosis of OUD;

(c) Enrolled in oral methadone, buprenorphine or buprenorphine-naloxone treatment for 6≥ weeks;

(d) Self-reported use of heroin and/or cocaine (verified by urine drug screen toxicology test);

(e) Voluntarily seeking continued treatment and able to attend the clinic as required in the protocol;

(f) Stable accommodation;

(g) Able to communicate verbal understanding of study material and protocol in English;

(h) Possession of a personal phone and ability to nominate at least one locator individual to assist with arranging research appointments.

Exclusion criteria

Otherwise eligible individuals will be excluded from the trial for any of the following:

(a) Clinically significant physical health conditions that may compromise safety or study conduct;

(b) Suicide planning (past 30 days) or suicide attempt (past six months);

(c) Clinically significant or uncontrolled mental health problems (including but not limited to psychosis, bipolar disorder, schizoaffective disorder) and/or history or evidence of organic brain disease or dementia that may compromise safety or compliance with the study protocol;

(d) Current legal proceedings which are likely to result in imprisonment or relocation outside of the centre's catchment area;

(e) Participation in a SUD treatment intervention study in past six months.

Table 2
Study timeline and measures

R														
	Baseline	**Study Week** (from randomisation to follow-up assessment)												
		IT												
Activity/measure		1-6	7	8	9	10	11	12	13	14	15	16	17	18-20
Screening for eligibility	X													
Medical/social history	X													
UDS		X				X				X				X
MINI														
- major depressive	X													
- suicidality	X													
- panic	X													
- post-traumatic stress	X													
- anti-social personality	X													
MINI														
- opioid	X													
- cocaine	X													
- alcohol	X													
PDS	X													
BPAQ-SF	X													
BIS-11	X													
TOP (heroin/cocaine)	X	X				X				X				X
MoCA (version 7.1)	X													
MoCA (version 7.2)														X
MCS-H	X	X				X				X				X
MCS-C	X	X				X				X				X
PHQ-9	X													X
GAD-7	X													X
WSAS														
ADSUS	X													X
EQ-5D-3L	X													X
OAT medication	X													
OAT dose *	X													X
Biomarker sampling	X													X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events form		X	X	X	X	X	X	X	X	X	X	X	X	X
PSI duration/content		X	X	X	X	X	X	X	X	X	X	X	X	X
SRS		X	X	X	X	X	X	X	X	X	X	X	X	X
ORS		X	X	X	X	X	X	X	X	X	X	X	X	X
Participant payments **	£20					£5				£5				£30

Note: R, randomisation; IT, initiation of treatment (weeks 1-6);
UDS, urine drug screen; MINI, Mini International Neuropsychiatric Interview; PDS, personality disorders screener; BPAQ-SF, Short-form Buss-Perry Aggression Questionnaire; BIS-11, Barratt Impulsiveness Scale; TOP, treatment outcomes profile;; MoCA, Montreal Cognitive Assessment; MCCS, Minnesota Craving Scale, MCS-C [cocaine]; MCS-H [heroin]; PHQ-9, Patient Health Questionnaire; GAD-7, Generalized Anxiety Disorder Scale; WSAS, Work and Social Adjustment Scale; AD-SUS, Adult Service Use Schedule; OAT, opioid agonist treatment; ORS, Outcome Rating Scale (PSI only). SRS, Session Rating Scale (PSI only); * OAT additionally recorded as highest/lowest dose and any medication change between baseline and final follow-up; ** shop-store vouchers to value shown for completion of research measures.

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